

# Recurrent vaginal candidosis: prospective study of effectiveness of maintenance miconazole treatment

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**SUMMARY** In a prospective study, 100 women with recurrent vaginal candidosis were treated with miconazole, using two 100 mg vaginal pessaries a day for one week, then one pessary twice a week for three months followed by one pessary a week for a further three months. Fifty four women elected to continue using one pessary a week for longer than six months.

Symptomatic vaginal candidosis did not occur in any patient during regular maintenance treatment. Of the 46 women who discontinued treatment before six months, however, 22 had a recurrence.

Maintenance prophylactic treatment with miconazole pessaries appears to be an acceptable and effective method of preventing recurrent episodes of vaginal candidosis.

Vaginal candidosis is the commonest genital infection in women, and a proportion of women go on to develop recurrent disease. It is not known why some women develop recurrent attacks, although the pathogenicity of *Candida albicans* in the vagina was recently the subject of extensive review.<sup>1</sup> One of the interesting theories proposed is that recurrent vaginal candidosis may be associated with disordered carbohydrate metabolism,<sup>2</sup> perhaps locally, but no single cause has yet been defined.

Acute vaginal candidosis can be treated simply and effectively with one of several antifungal agents, but the acute treatment regimens used seem not to influence the development of recurrent disease. Managing patients with recurrent disease has been less well studied than treatment of acute episodes. In a double blind placebo controlled study, Davidson and Mould showed that intermittent prophylactic treatment with clotrimazole pessaries and cream kept symptoms to an acceptable level in women with recurrent vaginal candidosis.<sup>3</sup> That study suggested that prophylactic treatment may be of value in such patients, but an unexpected finding was that prophylaxis did not prevent the return of yeasts to the vagina.

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An alternative approach has been to use ketoconazole, an orally active antifungal agent. Recurrence of symptomatic vaginal candidosis is seen, however, after short treatment courses lasting five<sup>4</sup> or 10 days,<sup>5</sup> and treatment courses of up to eight weeks have been advocated.<sup>6</sup> Prophylactic ketoconazole has also yielded highly encouraging results, whether given as a five day course at the start of each menstrual cycle or on a daily basis.<sup>7</sup> Sobel showed the effectiveness of maintenance prophylactic treatment with oral ketoconazole, although liver function tests need to be undertaken routinely.<sup>8</sup>

We studied 183 women with recurrent vaginal candidosis who received prophylactic courses of miconazole pessaries, and in this paper we report our findings in the first 100 to have been followed up for one year.

## Patients and methods

### STUDY POPULATION

We studied 100 women aged 18 to 45, who were outpatients at the department of genitourinary medicine of this hospital. All had recurrent vaginal candidosis, which was defined as at least two culture proved episodes in the previous 12 months. At the time of entry to the study all patients had acute vaginal candidosis, with symptoms of itching and soreness, signs of vulvovaginitis, and a positive candida culture. We excluded patients with mixed vaginal infections, known hypersensitivity to imidazole antifungals, or who had received antifungal treatment in the 14 days

preceding entry to the study. We also excluded pregnant women and those intending to become pregnant during the course of the study. Patients were not asked to change their contraceptive method, diet, clothing, or hygiene routines. Their sexual partners were not seen or treated routinely. The study protocol was approved by the hospital Ethical Committee, and informed consent was obtained from all patients.

#### SCHEDULE OF TREATMENT

Each patient received a seven day treatment course of two miconazole 100 mg (Gyno-Daktarin) vaginal pessaries a night, and was instructed to continue to use one pessary twice a week for three months, then one pessary a week thereafter for a further three months. Patients could elect to continue maintenance treatment for longer than six months.

#### ASSESSMENTS

Patients were assessed on entry to the study, at weeks 7 and 14, and then at intervals of three months. The first 51 patients were also seen after one week of treatment. All were asymptomatic, however, except for two with mild persistent vulval irritation, and all had negative cultures for *Candida* spp, so the remaining patients were not seen until the seven week assessment. All 100 patients were assessed at week 7 having continued prophylaxis for at least that time.

At each assessment, a standard history was recorded and genital examination performed. Special attention was paid to symptoms of itching, soreness, or vaginal discharge and to signs of vulvovaginitis, mucosal oedema, or the presence and nature of abnormal vaginal discharge. Patients with these symptoms and signs who had a positive culture for *Candida* spp were defined as having symptomatic vaginal candidosis. Vaginal specimens were taken with plastic loops for microscopy of wet film and Gram stained smears. The finding of budding yeasts and germ tubes on microscopy provided presumptive evidence of candidal infection. A further vaginal specimen was taken with a charcoal swab and placed in Stuart's medium for transport to the laboratory. The specimen for culture was plated on Sabouraud's agar and incubated at 37°C. Yeasts that grew within 48 hours were identified by routine methods, including germ tube tests.

## Results

#### STUDY POPULATION

Table 1 shows the demographic data of the first 100 patients studied. Twenty three had attended the clinic previously with a history of recurrent vaginal candidosis, and the remaining 77 were attending for the first time with this condition. Patients were generally

Table 1 *Clinical characteristics of 100 patients with recurrent vaginal candidosis. (Figures are numbers of patients unless otherwise stated)*

Characteristics	Patients studied
Mean age (years)	26.0
Mean length of history (months)	39.4
Marital status:	
Married	48
Single	52
History of balanoposthitis in male partners	26
Type of contraceptive used:	
Oral	61
Other	39
Underlying medical disorder:	
Diabetes	3
Recurrent urinary tract infection	2
Others	2

in their twenties or thirties, and most used oral contraceptives. Two had underlying disease other than diabetes; one had a history of renal disease and one of ulcerative colitis, but both were healthy at the time of the study. Two patients were taking prophylactic antibiotics throughout the study because of recurrent urinary tract infection. They remained on maintenance treatment throughout the study, and did not experience any recurrence of vaginal candidosis. Compared with patients who had attended previously, more first time attenders were married and had a shorter history of disease. The 23 patients who had attended previously had made a total of 148 previous visits for recurrent vaginal candidosis in 648 patient months, which was equivalent to one recurrent attack a patient every 4.4 months.

#### OUTCOME OF TREATMENT

Of the 100 patients entering the study, 75 were followed up for more than six months. These 75 women consisted of 54 who continued maintenance treatment for longer than six months and 21 of the 22 who discontinued treatment before six months and returned with symptomatic recurrent candidosis. These 21 patients with recurrences were treated again and continued receiving maintenance treatment, but are evaluated in this study up to their recurrent episode only. They remained free of attacks, however, while receiving maintenance treatment. The one other of the

Table 2 *Duration of maintenance treatment and times to recurrence of vaginal candidosis*

Duration of maintenance treatment	No (%) with recurrences/No treated	Mean time to recurrence after treatment stopped
< 6 months	22/46 (48)	3.0 months
6-12 months	7/29 (24)	3.9 months
12 months	0/25	0

Table 3 Time from stopping treatment to recurrence in 29 women

Duration of treatment	No with recurrence at (months after stopping treatment):									Total
	1	2	3	4	5	6	7	8	9	
<6 months	8	3	3	2	3	1	1	1		22
>6 months		2	1	1	2	1				7

22 women with recurrences attended irregularly and is not evaluated after recurrence.

The patient population divided into two groups; the 54 who completed at least six months treatment, and 46 who stopped before six months. Of the 46 who discontinued prophylactic treatment within six months, 22 subsequently attended again with a recurrence that was confirmed by culture. The mean time to clinical recurrence after stopping maintenance treatment in this group was 3.0 months (table 2). Table 3 shows the detailed times to recurrence.

Fifty four patients persisted with prophylaxis for at least six months, and 25 of them continued treatment for 12 months. Seven of the 29 patients who discontinued treatment after six months attended again with a recurrence (symptoms and signs of vulvovaginitis and a positive culture for *Candida* spp). The mean time from stopping prophylaxis to experiencing clinical recurrence in this group was 3.9 months (tables 2 and 3). Two of the seven recurrences were caused by *Candida glabrata*, which was cultured at nine and 12 months after the patients' entry into the study.

Occasional irritation and discharge was reported at week 7 by five patients. All had negative cultures for *Candida* spp, but three had vulvitis. One further patient who remained symptomless while receiving maintenance treatment had a positive culture for *C. albicans* at week 7, but no symptoms or signs of vulvitis or vaginitis. This one apparent recolonisation during continuous maintenance treatment was no longer present at the 14 week assessment.

No patient, including the 25 women who continued prophylaxis for 12 months, developed symptomatic vaginal candidosis while receiving maintenance treatment.

#### ADVERSE REACTION

Mild irritation was reported by 21 patients, nine of whom discontinued prophylaxis before six months. All of these patients yielded negative cultures for *Candida* spp, and their symptoms cleared spontaneously or responded rapidly to external application of hydrocortisone (1%) and miconazole (2%). Two patients reported an apparently allergic reaction to oral miconazole, which led to discontinuation of treatment. One other patient discontinued treatment

before six months, having elected to receive specific treatment for any recurrence rather than persisting with prophylaxis.

#### Discussion

Numerous studies of the pathogenesis of vaginal candidosis have been undertaken, and many different theories have been proposed to explain why some women go on to develop recurrent disease.<sup>19</sup> Until the cause of recurrent vaginal candidosis is understood, however, managing patients with this unpleasant condition will rely heavily on antifungal treatment. The few published studies on drug treatment of patients suffering recurrences indicate that regular prophylactic treatment may offer a means of greatly reducing recurrences in such patients.<sup>3,7,8</sup>

The first study that showed the efficacy of long term cyclical prophylaxis was reported by Davidson and Mould, who used topical clotrimazole treatment.<sup>3</sup> They showed that prophylaxis reduced the attack rate of vaginal candidosis as long as the medication was given. The pattern of recurrent infection returned, however, once treatment was stopped. Similarly, Sobel has shown that cyclical prophylaxis with oral ketoconazole reduced the incidence of recurrences as long as it was given, but that candidosis soon returned after treatment was stopped.<sup>7</sup> Continuous daily prophylaxis with oral ketoconazole was also effective in preventing recurrent infection, but soon after treatment stopped nearly half the patients treated had recurrent candidosis.<sup>8</sup>

The study published here was designed to assess the suitability of the regular use of miconazole pessaries as a means of prophylaxis in women with recurrent vaginal candidosis. During maintenance treatment symptomatic vaginal candidosis did not occur, but relapse was common after prophylaxis stopped. Thus regular use of miconazole pessaries can reduce the recurrence rate, but prolonged prophylactic courses may not have any long lasting benefit after treatment stops.

Long term prophylaxis with any imidazole antifungal agent carries the theoretical risk that resistance to the drug may emerge during its prolonged use. Although future drug sensitivity studies are required, there are only four well substantiated reports of drug resistance to azole antifungals emerging during clinical use.<sup>10</sup> The risk of emergent resistance to the drug is therefore small and should not prevent further clinical studies of imidazole prophylaxis. Apart from some cases of minor irritation, the only side effects reported by our patients were two cases of allergic reaction. Such reactions are described in the manufacturer's data sheet (Gyno-Daktarin; Janssen Pharmaceutical, Wantage, Oxfordshire, England), and have also been

reported previously (unpublished observation, Janssen Pharmaceuticals). In view of the dramatic reduction in recurrences achieved by prophylaxis, the reported level of side effects is acceptable and not regarded as a cause for concern. In contrast, oral ketoconazole causes symptoms of mild toxicity, such as nausea,<sup>8</sup> and also carries the risk of hepatitis.<sup>11</sup>

This study shows that symptomatic vaginal candidosis does not occur during regular long term prophylaxis with one or two miconazole pessaries a week. Women are pleased and relieved at their lack of symptoms that previously caused much distress in their personal and sexual lives. Some women do suffer recurrent attacks soon after prophylaxis is discontinued. Those women can be identified, and it may be worthwhile continuing their maintenance treatment for many more months with one pessary a week. Long term maintenance treatment with miconazole pessaries appears to be highly effective in reducing the incidence of recurrent vaginal candidosis. It is also acceptable to patients.

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